

Monitoring Potential Neurotoxic Effects of Hazardous Waste Disposal

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This report reviews neurotoxicological principles relevant to situations of hazardous waste disposal. Some of the diagnostic techniques currently used for field assessment of nervous system dysfunction are critically evaluated. These include nerve conduction velocity, evoked potentials, neuropsychological testing and use of the Optacon.

Hazardous waste disposal sites generally expose large populations to toxins. Although outbreaks of neurotoxicity have yet to be definitely linked to waste disposal sites, it is possible that such outbreaks may occur in the future. Several situations may be envisioned (1). The simplest situation would be human exposure to substances, such as mercury or kepone, that are known to produce characteristic neurological abnormalities. This situation is best met by surveying at-risk individuals for body fluid levels and neurological dysfunction (tremor, nystagmus). A more difficult problem is the appearance of neurological abnormalities in individuals exposed to chemicals not considered neurotoxic. Here one must carefully define the illness and then link it to one or more agents by experimental animal studies.

The present report reviews neurotoxicological factors relevant to this problem and discusses the techniques commonly used to assess individuals exposed to known neurotoxins.

Neurotoxicological Factors

Substances that produce structural change in the nervous system usually result in diffuse disease of susceptible subsystems. Especially vulnerable subsystems are: peripheral nerves, long pathways of the spinal cord, the cerebrum and the cerebellum.

Focal or asymmetrical disorders of these structures (e.g., aphasia, mononeuropathy) are generally not of toxic origin. Toxic neurologic disease may profitably be considered to reflect attack on various components of nervous tissue: axons, neurons, myelin, glial and blood vessels. The first two components are especially important, and when attacked, the resulting diseases are called toxic axonopathy and toxic neuronopathy. The specific clinical, pathological and physiological characteristics of these conditions have been recently reviewed (2).

The biochemical basis of most neurotoxic conditions is unknown, and the chemical formula of an untested substance is frequently not predictive of neurotoxicity. For example, it is now clear that the gamma-diketone moiety is an essential feature underlying aliphatic hexacarbon neurotoxicity. If the two keto groups are differently spaced in the molecule, the compound is frequently harmless (e.g., 2,5-heptanedione is neurotoxic, 2,6-heptanedione is not).

Acute and chronic exposure to the same substance may result in a dramatically variable clinical picture (e.g., acute high-level exposure to acrylamide causes a toxic encephalopathy with convulsions and hallucinations, while low-level, chronic exposure causes distal axonopathy; also acute high-level exposure to *n*-hexane results in narcosis, but low-level, chronic exposure produces a distal axonopathy).

Subclinical or asymptomatic dysfunction of the nervous system can occur and may go undetected for a prolonged time.

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Noninvasive Neurodiagnostic Techniques

There are formidable obstacles in screening for toxic disease of the nervous system, especially when compared to more accessible, readily monitored systems (e.g., blood, skin). In addition, the most accurate noninvasive diagnostic techniques (e.g., computerized imaging), aimed at structural or vascular abnormalities, are of limited use in neurotoxicology. The clinical neurotoxicologist usually must rely heavily on the limited tools of physical examination, clinical electrophysiology and neuropsychology. Nerve conduction velocity and evoked potential studies are among the most widely employed electrophysiological maneuvers to detect peripheral and central nervous system dysfunction.

Behavioral or cognitive disturbances are usually evaluated by standard psychological tests modified for rapid screening of large populations. This section briefly reviews the use and misapplication of these techniques.

Determinations of nerve conduction velocity are now routinely used for the assessment of peripheral neuropathy. Measurement of motor conduction velocity is simple, noninvasive, can be performed with portable equipment and is widely employed in field assessment of polyneuropathy. Maximal motor nerve conduction velocity is determined by percutaneous stimulation of a mixed peripheral nerve at two or more proximal sites while recording the onset latency of an evoked muscle action potential by surface electrodes from a distal muscle. Sensory conduction studies may also use cutaneous stimulation, surface electrodes and standard oscilloscope recording; however, response variability is frequent when the test is performed under these conditions. Such studies record only the largest diameter myelinated fibers, and these may or may not be affected. Optimal assessment of peripheral nerve function requires the use of multiple stimuli and averaging techniques, which define the wave shape of the compound nerve action potential. The total distribution of conduction velocities can be calculated from the average wave form. Under these latter conditions, the assessment of sensory nerve function becomes a powerful diagnostic tool. Other valuable electrodiagnostic techniques such as the collision procedure (for detecting small-fiber dysfunction), stimulus trains, F-wave studies and assessment of the H-reflex (for assessing proximal conduction velocity) are also available but rarely used in field studies.

Axonal neuropathies, in their early stages, generally produce only slight slowing of motor and

sensory conduction which may be limited to a specific subset of axons (e.g., large-diameter myelinated fibers). In addition, many common neurotoxic substances produce distal axonal degeneration, so that nerve-conduction studies at proximal sites are of limited value. The range of values for motor and sensory conduction velocities and sensory amplitude is large (as performed under field conditions), and minor variations in nerve conduction velocity are subject to over interpretation unless scrupulously controlled. In sum, considerable expertise, mature judgment and the appropriate equipment are required to select and perform the correct procedures and interpret data from nerve conduction studies accurately. Whenever possible, such studies should be performed in a modern, well-equipped electrodiagnostic laboratory that routinely utilizes averaging techniques and has extensive experience with normal individuals. Many reported field studies appear poorly controlled and are seriously flawed by inadequate sampling that does not permit statistical analysis. The Danish report of lead-exposed workers stands as an example of a meticulous peripheral electrodiagnostic study, whose data can withstand considerable statistical scrutiny (3).

Recent advances in computer-averaged evoked potentials enable the noninvasive recording of synchronous activity at a distance from its source within the nervous system. Such "far-field" data principally reflect afferent activity within fiber tracts and can be combined with previously defined components of cortical origin to provide a complete index of the integrity of each of the major sensory systems. The possible effects of *n*-hexane (4), xylene and alcohol (5) on the human visual system, and those of lead (6) on the somatosensory system, have been investigated in man by using the evoked potential technique. Both amplitude and latency measures have been employed in human studies, but the latency measures appear more reliable. Spatio-temporal analysis of surface-recorded evoked potentials has permitted monitoring portions of tracts most vulnerable to specific toxicants. Our recent work in the monkey, utilizing lower-extremity stimulation, has demonstrated that the distal extreme of axons within the long pathways of the *gracile fasciculus* show early degeneration following exposure to acrylamide (6).

It is hoped that similar techniques to test humans exposed to neurotoxins will become feasible. The use of evoked potentials as a neurological screening procedure appears limited both by the variability of this measure when applied to populations at large and the current lack of standard recording procedures among laboratories. The latency and ampli-

tude of far-field components are significantly influenced by the age, skin temperature and size of the subject, while cortical components are additionally influenced by the precise location of the recording electrode and the attention level of the individual.

Neuropsychological deficits that have been reported in association with exposure to toxicants include: disturbances in intelligence, memory, and problem solving as well as alterations in attention, psychomotor functioning and mood (8,9). Detection of these effects in a large, previously unstudied population is difficult. Clinical evaluation of case histories can help in determining the extent of these problems; but this often is highly subjective and descriptions of the symptoms are usually vague. Subtle alterations in psychological functioning clearly can go unnoticed by both physician and subject. Psychological evaluation, using a battery of standard tests, is the only available procedure capable of providing objective and quantifiable results regarding behavioral deficits. Selection of the appropriate test is critical because of the considerable time requirements for this form of evaluation and should be based on a careful review of preliminary observations. A common misuse of neuropsychological testing is overinterpretation of selected portions of the data. The quantitative results are often quite variable both within and across subject measurements. Additional problems are absence of standardization and nonspecificity of many of the available tests. Since psychological data can be significantly influenced by the predisposition of both subject and experimenter, these tests should be scored in a double-blind fashion. Whenever possible, psychological data should be correlated with biochemical or physiological findings. The recent study of memory performance in polybrominated biphenyl (PBB)-exposed individuals exemplifies a carefully controlled and well-executed investigation of neuropsychological status and should serve as a model for future work in this area (10). In this study, 46 subjects were examined by using six memory tests; the body burden of chemical was monitored by chemical analysis of fat biopsies, and the psychological data were subjected to the appropriate multivariate analysis. In sum, it is apparent that techniques currently used in neurotoxicity screening programs are crude, subject to variation and frequently misinterpreted or wrongly applied.

Screening can be much more effective if the diagnostic technique is targeted at a specific function vulnerable to the neurotoxin in question. For example, we have recently designed a rapid, reliable and quantifiable test of fingertip sensation that may prove applicable in screening programs for

some neurotoxins (11). The rationale for this test was derived from our experimental studies of acrylamide-intoxicated cats, which indicated that the most sensitive structure was the axon of the toe-pad Pacinian corpuscle (12,13). The appropriate clinical manifestation of such early pathophysiological changes would be loss of vibration sense. Since the Pacinian corpuscle was so exquisitely vulnerable, and elevation of vibratory threshold is a feature common to several toxic neuropathies, we elected to monitor vibration sensation. We tested the modified Optacon, a portable electronic device which, in its unmodified state, converts visual images into tactile forms. The instrument is designed for use by blind persons, who rest their index finger-pad on a grid composed of 144 small metal rods which vibrate. Baseline testing was performed on 124 subjects; a normal group of 52 male and 48 females, and a clinical group of 11 males and 13 females undergoing treatment for diabetes (a common cause of peripheral neuropathy). In normal subjects there was striking consistency in the mean sensory threshold determined at various times and a linear increase in threshold with age. The diabetic population was more variable and contained several subjects with markedly elevated thresholds. The study suggested the potential usefulness of the modified Optacon as a simple, reliable technique for detecting sensory loss and abnormal metabolic or toxic conditions. Recently, nurses in chemical plants have been trained to field test individuals and have obtained reliable (14) thresholds. Four data points are collected per annum for each subject. It is hoped that the Optacon will also prove useful in certain specialty medical clinics (diabetes, renal, oncology), where individuals susceptible to distal axonopathy require frequent assessment in a longitudinal fashion.

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